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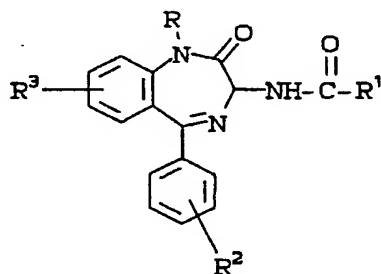
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(54) Cholecystokinin antagonists.

(57) Benzodiazepine analogs of the formula :



I

are disclosed which are antagonists of gastrin and cholecystokinin (CCK).

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FIELD OF THE INVENTION

This invention relates to the discovery of Benzodiazepine analogs of Formula I for use as antagonists of cholecystokinin (CCK) and gastrin when administered to animals, preferably humans.

BACKGROUND OF THE INVENTION

The Benzodiazepine analogs of Formula I of this invention are useful in treating various diseases caused by an excess of CCK or gastrin. Cholecystokinins (CCK) and gastrin are structurally related neuropeptides which exist in gastrointestinal tissue and in the central nervous system (see, V. Mutt, Gastrointestinal Hormones, G.B.J. Glass, Ed., Raven Press, NY, p. 169 and G. Nilsson, ibid., p. 127).

Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form (see, Mutt and Jorpes, Biochem. J. **125**, 678 (1971)), its carboxyl terminal octapeptide, CCK-8 (also a naturally-occurring neuropeptide and the minimum fully active sequence), and 39- and 12-amino acid forms. Gastrin occurs in 34-, 17- and 14-amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH₂, which is the common structural element shared by both CCK and gastrin.

CCK's are believed to be physiological satiety hormones, thereby possibly playing an important role in appetite regulation (G. P. Smith, Eating and Its Disorders, A. J. Stunkard and E. Stellar, Eds, Raven Press, New York, 1984, p. 67), as well as also stimulating colonic motility, gall bladder contraction, pancreatic enzyme secretion, and inhibiting gastric emptying. They reportedly co-exist with dopamine in certain mid-brain neurons and thus may also play a role in the functioning of dopaminergic systems in the brain, in addition to serving as neurotransmitters in their own right (see: A. J. Prange et al., "Peptides in the Central Nervous System", Ann. Repts. Med. Chem. **17**, 31, 33 [1982] and references cited therein; J. A. Williams, Biomed. Res. **3** 107 [1982]; and J. E. Morley, Life Sci. **30**, 479, [1982]).

The primary role of gastrin, on the other hand, appears to be stimulation of the secretion of water and electrolytes in the stomach, and, as such, it is involved in control of gastric acid and pepsin secretion. Other physiological effects of gastrin then include increased mucosal blood flow and increased antral motility. Rat studies have shown that gastrin has a positive trophic effect on the gastric mucosa, as evidenced by increased DNA, RNA and protein synthesis. See e.g. U.S. Serial No. 452,023, corresponding to EP-A-0434364.

Antagonists to CCK and to gastrin have been useful for preventing and treating CCK-related and/or gastrin-related disorders of the gastrointestinal (GI) and central nervous (CNS) systems of animals, preferably mammals, and especially those of humans. Just as there is some overlap in the biological activities of CCK and gastrin, antagonists also tend to have affinity for both receptors. In a practical sense, however, there is enough selectivity for the different receptors that greater activity against specific CCK- or gastrin-related disorders can often also be identified.

Selective CCK antagonists are themselves useful in treating CCK-related disorders of the appetite regulatory systems of animals as well as in potentiating and prolonging opiate-mediated analgesia, thus having utility in the treatment of pain [see P. L. Faris et al., Science **226**, 1215 (1984)]. Selective gastrin antagonists are useful in the modulation of CNS behavior, as a palliative for gastrointestinal neoplasms, and in the treatment and prevention of gastrin-related disorders of the gastrointestinal system in humans and animals, such as peptic ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia and other conditions in which reduced gastrin activity is of therapeutic value. See e.g. U.S. Patent 4,820,834. It is further expected that the CCK antagonists of Formula I are useful anxiolytic agents particularly in the treatment of panic and anxiety disorders.

Since CCK and gastrin also have trophic effects on certain tumors [K. Okyama, Hokkaido J. Med. Sci., **60**, 206-216 (1985)], antagonists of CCK and gastrin are useful in treating these tumors [see, R.D. Beauchamp et al., Ann. Surg., 202,303 (1985)].

Distinct chemical classes of CCK-receptor antagonists have been reported [R. Freidinger, Med. Res. Rev. **9**, 271 (1989)]. The first class comprises derivatives of cyclic nucleotides, of which dibutyryl cyclic GMP has been shown to be the most potent by detailed structure-function studies (see, N. Barlas et al., Am. J. Physiol., **242**, G 161 (1982) and P. Robberecht et al., Mol. Pharmacol., **17**, 268 (1980)).

The second class comprises peptide antagonists which are C-terminal fragments and analogs of CCK, of which both shorter (Boc-Met-Asp-Phe-NH₂, Met-Asp-Phe-NH₂), and longer (Cbz-Tyr(SO₃H)-Met-Gly-Trp-Met-Asp-NH₂) C-terminal fragments of CCK can function as CCK antagonists, according to recent structure-function studies (see, R. T. Jensen et al., Biochem. Biophys. Acta., **757**, 250 (1983), and M. Spanarkel et al., J. Biol. Chem., **258**, 6746 (1983)). The latter compound was recently reported to be a partial agonist [see, J. M. Howard et al., Gastroenterology **86**(5) Part 2, 1118 (1984)].

The third class of CCK-receptor antagonists comprises the amino acid derivatives: proglumide, a derivative of glutamic acid, and the N-acyl tryptophans including para-chlorobenzoyl-L-tryptophan (benzotript), [see,

W. F. Hahne *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, **78**, 6304 (1981), R. T. Jensen *et al.*, *Biochem. Biophys. Acta.*, **761**, 269 (1983)]. All of these compounds, however, are relatively weak antagonists of CCK (IC₅₀: generally 10⁻⁴M [although more potent analogs of proglumide have been recently reported in F. Makovec *et al.*, *Arzneim-Forsch Drug Res.*, **35** (II), 1048 (1985) and in German Patent Application DE 3522506A1], but down to 10⁻⁶M in the case of peptides), and the peptide CCK-antagonists have substantial stability and absorption problems.

In addition, a fourth class consists of improved CCK-antagonists comprising a nonpeptide of novel structure from fermentation sources [R. S. L. Chang *et al.*, *Science*, **230**, 177-179 (1985)] and 3-substituted benzodiazepines based on this structure [published European patent Applications 167 919, 167 920 and 169 392, B. E. Evans *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, **83**, p. 4918-4922 (1986) and R.S.L. Chang *et al.*, *ibid.*, p. 4923-4926] have also been reported.

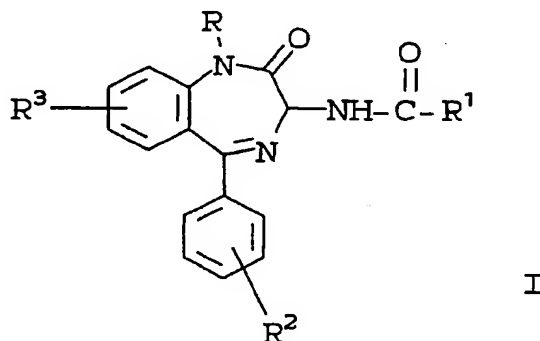
No really effective receptor antagonists of the *in vivo* effects of gastrin have been reported (J. S. Morley, *Gut Pept. Ulcer Proc.*, Hiroshima Symp. 2nd, 1983, p. 1), and very weak *in vitro* antagonists, such as proglumide and certain peptides have been described [(J. Martinez, *J. Med. Chem.*, **27**, 1597 (1984)]. Recently, however, pseudopeptide analogs of tetragastrin have been reported to be more effective gastrin antagonists than previous agents [J. Martinez *et al.*, *J. Med. Chem.*, **28**, 1874-1879 (1985)].

A new class of Benzodiazepine antagonist compounds has further been reported which binds selectively to brain CCK (CCK-B) and gastrin receptors [see M. Bock *et al.*, *J. Med. Chem.*, **32**, 13-16 (1989)]. One compound of interest reported in this reference to be a potent and selective antagonist of CCK-B receptors is (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N¹-(3-methylphenyl) urea (See U.S. Patent 4,820,834.) One disadvantage of the new CCK-B compound reported in Bock *et al.*, *J. Med. Chem.*, **32**, 13-16 (1989) and U.S. Patent 4,820,834, is that these CCK-B compounds are poorly water soluble.

It is, therefore, an object of the present invention to provide antagonists of CCK and gastrin. If an antagonist compound could be prepared which would bind with the cell surface receptor of CCK or gastrin, then the antagonist compounds of this invention could be used to block the effect of CCK and gastrin. Another object of the present invention is to provide novel CCK and gastrin antagonist compounds which are water soluble. Other objects of the present invention are to provide methods of inhibiting the action of CCK and gastrin through the administration of novel benzodiazepine analog compounds. The above and other object are accomplished by the present invention in the manner more fully described below.

SUMMARY OF THE INVENTION

The present invention provides Benzodiazepine analogs of the formula:

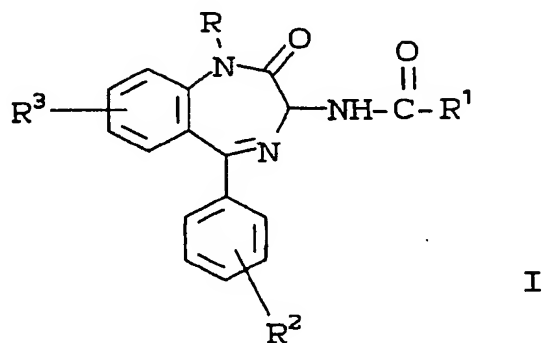


for use as antagonists of CCK and gastrin. The above-mentioned compounds can be used in a method of acting upon a CCK and/or gastrin receptor which comprises administering a therapeutically effective but non-toxic amount of such compound to an animal, preferably a human. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, dispersed therein, an effective but non-toxic amount of such compound is another aspect of this invention.

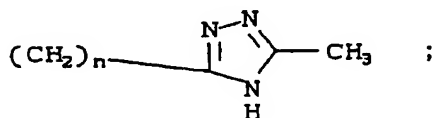
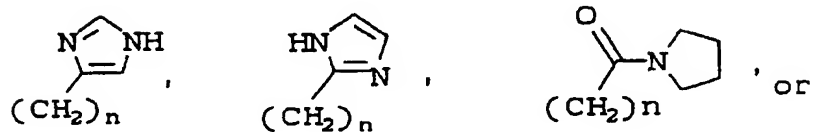
DETAILED DESCRIPTION OF THE INVENTION

Benzodiazepine analogs of Formula I provide antagonists of CCK and gastrin. The present invention further provides novel CCK and gastrin antagonist compound which are water soluble. The Benzodiazepine analogs of Formula I are useful in a method of antagonizing the binding of CCK to CCK receptors or antagonizing the

binding of gastrin to gastrin receptors. The novel Benzodiazepine analogs of the present invention are illustrated by compounds having the formula:



wherein:
R is

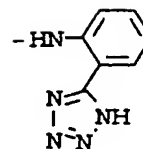
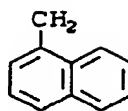
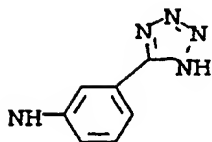


R¹ is

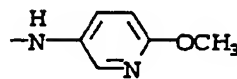
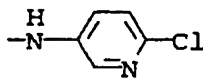
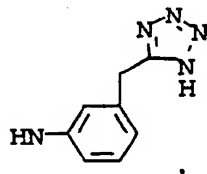
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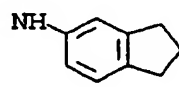
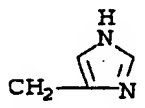
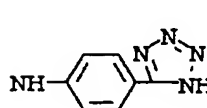
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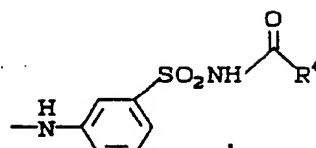
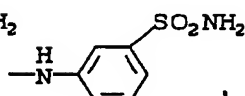
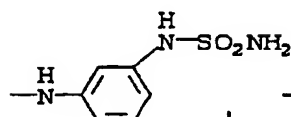
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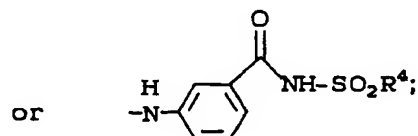
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R⁴ is C₁-C₆ straight or branched chain alkyl, CF₃, cyclopropyl, 2,2-dimethyl cyclopropyl, 2,2-difluorocyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or mono- or di-substituted phenyl, wherein the substitution is F, Cl, Br, CN, NO₂, CF₃, OCH₃, or NH₂; and
n is 1, 2 or 3;

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The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bungeard, Elsevier, 1985.

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such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

5 The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

10 The pharmaceutically acceptable salts of the acids of Formula I are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

15 The compounds of Formula I antagonize CCK and/or gastrin and are useful as pharmaceutical agents for animals, preferably for mammals, and most especially for humans, for the treatment and prevention of gastrointestinal disorders and central nervous system disorders.

Examples of such gastrointestinal disorders include ulcers, such as peptic and gastrointestinal ulcers, irritable bowel syndrome, gastroesophageal reflux disease or excess pancreatic or gastrin secretion, acute pancreatitis, or motility disorders, Zollinger-Ellison syndrome, and antral and cell hyperplasia.

20 Examples of central nervous system disorders include central nervous system disorders caused by CCK interaction with dopamine, such as neuroleptic induced tardive dyskinesia, Parkinson's disease, schizophrenia, other psychosis or Gilles de la Tourette syndrome, and disorders of appetite regulatory systems.

25 The compounds of Formula I may further be useful in the treatment or prevention of additional central nervous system disorders including neurological and psychiatric disorders. Examples of such central nervous system disorders include anxiety disorders and panic disorders, wherein CCK and/or gastrin is involved. Additional examples of central nervous system disorders include panic syndrome, anticipatory anxiety, phobic anxiety, panic anxiety, chronic anxiety, and endogenous anxiety.

30 The compounds of Formula I may further be useful in the treatment of oncologic disorders wherein CCK or gastrin may be involved. Examples of such oncologic disorders include small cell adenocarcinomas and primary tumors of the central nervous system glial and neuronal cells. Examples of such adenocarcinomas and tumors include, but are not limited to, tumors of the lower esophagus, stomach, intestine, colon and lung, including small cell lung carcinoma.

35 The compounds of Formula I may further be used to control pupil constriction in the eye. The compounds may be used for therapeutic purposes during eye examinations and intraocular surgery in order to prevent miosis. The compounds may further be used to inhibit miosis occurring in association with iritis, uveitis and trauma.

The compounds of Formula I are also useful for directly inducing analgesia, opiate or non-opiate mediated, as well as anesthesia or loss of the sensation of pain.

40 The compounds of Formula I may further be useful for preventing or treating the withdrawal response produced by chronic treatment or abuse of drugs or alcohol. Such drugs include, but are not limited to cocaine, alcohol or nicotine.

45 The compounds of formula (I) may also be useful as neuroprotective agents, for example, in the treatment and/or prevention of neurodegenerative disorders arising as a consequence of such pathological conditions as stroke, hypoglycaemia, cerebral palsy, transient cerebral ischaemic attack, cerebral ischaemia during cardiac pulmonary surgery or cardiac arrest, perinatal asphyxia, epilepsy, Huntington's chorea, Alzheimer's disease, Amyotrophic Lateral Sclerosis, Parkinson's disease, Olivo-pontocerebellar atrophy, anoxia such as from drowning, spinal cord and head injury, and poisoning by neurotoxins, including environmental neurotoxins.

The present invention also encompasses a pharmaceutical composition useful in the treatment of CCK and/or gastrin disorders comprising the administration of a therapeutically effective but non-toxic amount of the compounds of Formula I, with or without pharmaceutically acceptable carriers or diluents.

50 The compounds of Formula I, may be administered to animals, preferably to mammals, and most especially to a human subject either alone or, preferably, in combination with pharmaceutically-acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including intravenous, intramuscular, intraperitoneal, subcutaneous and topical administration.

55 For oral use of an antagonist of CCK, according to this invention, the selected compounds may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents in-

clude lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

When a compound according to Formula I is used as an antagonist of CCK or gastrin in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms. However, in most instances, an effective daily dosage will be in the range of from about 0.005 mg/kg to about 50 mg/kg of body weight, and preferably, of from about 0.05 mg/kg to about 50 mg/kg of body weight, and most preferably, of from about 0.5 mg/kg to about 20 mg/kg of body weight, administered in single or divided doses.

In some cases, however, it may be necessary to use dosage levels outside these limits. For example, doses as low as about 1 ng/kg, about 0.005 µg to about 0.05 µg or about 100 ng to about 100 µg/kg may be administered.

In the effective treatment of panic syndrome, panic disorder, anxiety disorder and the like, preferably about 0.05 mg/kg to about 1.0 mg/kg of CCK antagonist may be administered orally (p.o.), administered in single or divided doses per day (b.i.d.). Other routes of administration are also suitable.

For directly inducing analgesia, anesthesia or loss of pain sensation, the effective dosage range is preferably from about 100 ng/kg to about 1 mg/kg by intraperitoneal administration. Oral administration is an alternative route, as well as others.

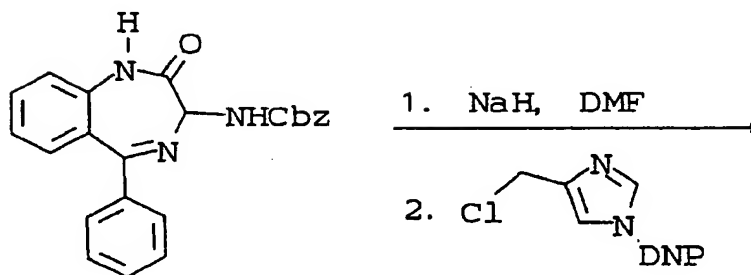
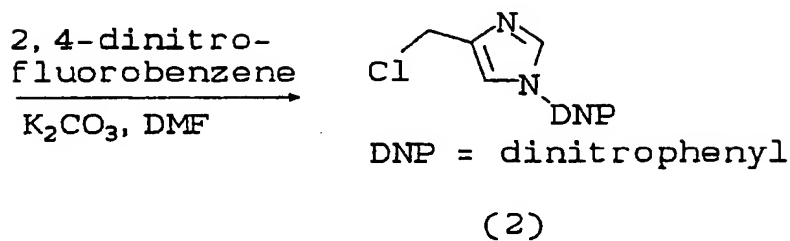
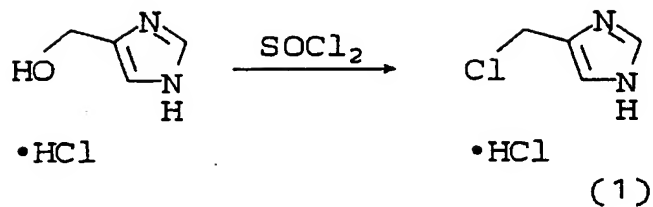
In the treatment of irritable bowel syndrome, preferably about 0.1 to 10 mg/kg of CCK antagonist is administered orally (p.o.), administered in single or divided doses per day (b.i.d.). Other routes of administration are also suitable.

The use of a gastrin antagonist as a tumor palliative for gastrointestinal neoplasma with gastrin receptors, as a modulator of central nervous activity, treatment of Zollinger - Ellison syndrome, or in the treatment of peptic ulcer disease, an effective dosage is preferably from about 0.1 to about 10 mg/kg, administered one-to-four times daily is indicated.

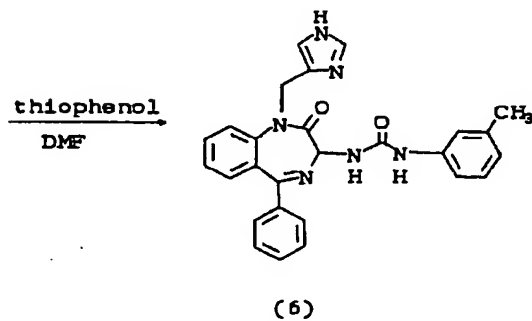
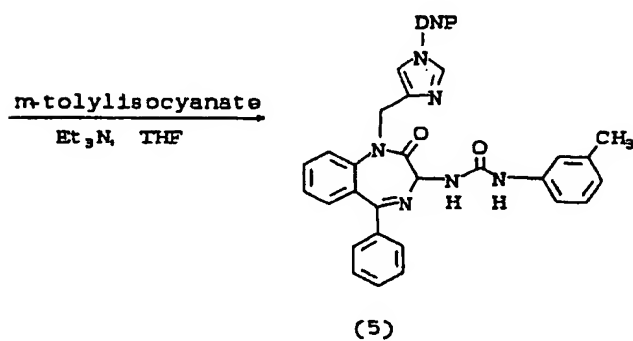
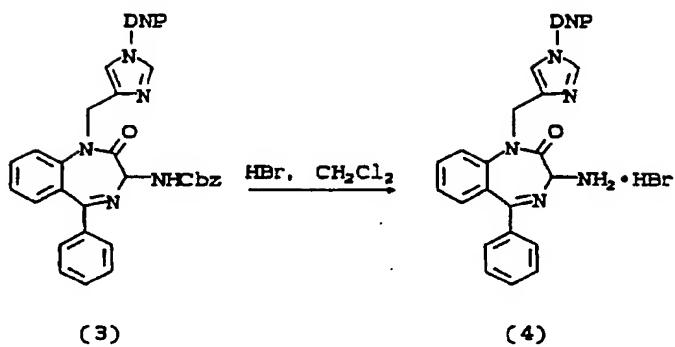
Because these compounds antagonize the function of CCK in animals, they may also be used as feed additives to increase the food intake of animals in daily dosage preferably from about 0.05 mg/kg to about 50 mg/kg of body weight.

The compounds of Formula I may be prepared according to the reaction schemes as set forth below.

SCHEME 1



SCHEME 1 (CONT'D)



SCHEME 2

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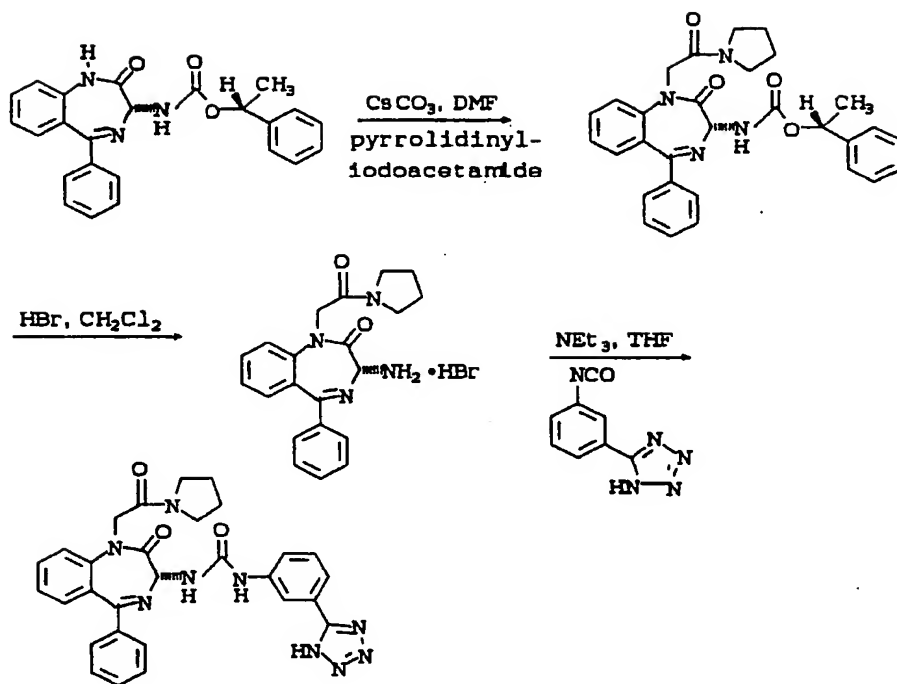
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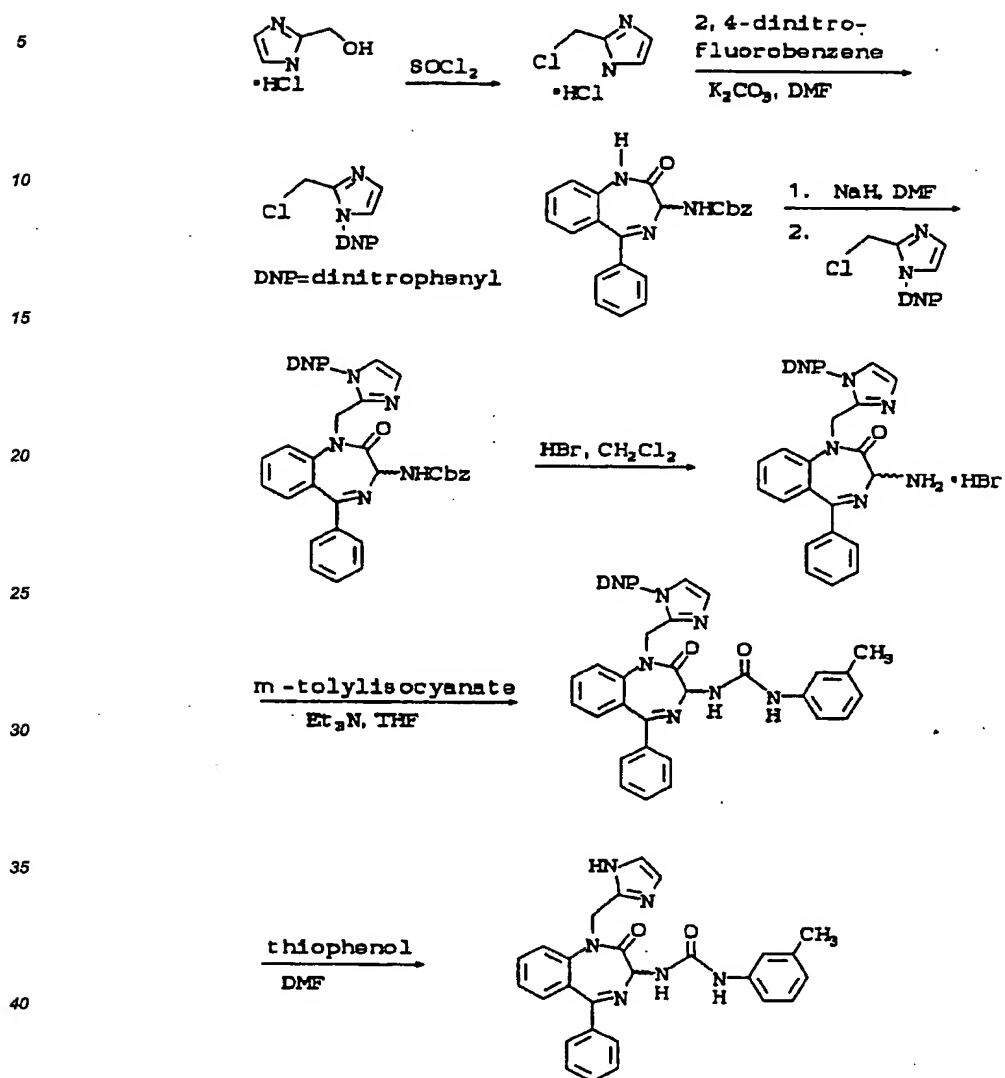
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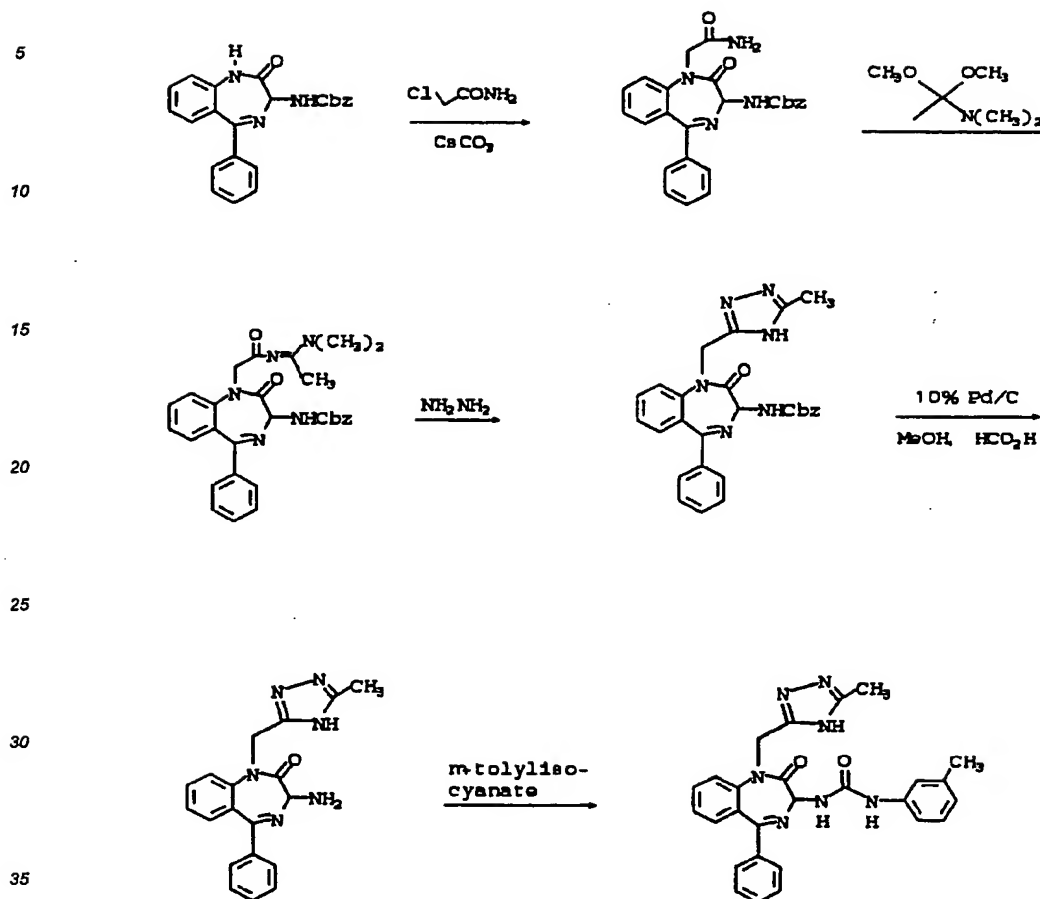
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SCHEME 3



Scheme 4



1. CCK Receptor Binding (Pancreas)

CCK-8 sulphated was radiolabelled with ^{125}I -Bolton Hunter reagent (2000 Ci/mmole). Receptor binding was performed according to Chang and Lotti (Proc. Natl. Acad. Sci. **83**, 4923-4926, 1986) with minor modifications.

Male Sprague-Dawley rats (150-200g) were sacrificed by decapitation. The whole pancreas was dissected free of fat tissue and was homogenized in 25 volumes of ice-cold 10 mM Hepes buffer with 0.1% soya bean trypsin inhibitor (pH 7.4 at 25°C) with a Kinematica Polytron. The homogenates were centrifuged at 47,800 g for 10 min. Pellets were resuspended in 10 volumes of binding assay buffer (20 mM Hepes, 1 mM EGTA, 5 mM MgCl_2 , 150 mM NaCl, bacitracin 0.25 mg/ml, soya bean trypsin inhibitor 0.1 mg/ml, and bovine serum albumin 2 mg/ml, pH 6.5 at 25°C) using a teflon homogenizer, 15 strokes at 500 rpm. The homogenate was further diluted in binding assay buffer to give a final concentration of 0.5 mg original wet weight/1 ml buffer. For the binding assay, 50 μl of buffer (for total binding) or unlabeled CCK-8 sulfated to give a final concentration of 1 μM (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ^{125}I -CCK binding) and 50 μl of 500 pM ^{125}I -CCK-8 (i.e. 50 pM final concentration) were added to 400 μl of the membrane suspensions in microfuge tubes. All assays were run in duplicate. The reaction mixtures were incubated at 25°C for 2 hours and the reaction terminated by rapid filtration (Brandell 24 well cell harvester) over Whatman GF/C filters, washing 3 x 4 ml with ice-cold 100 mM NaCl. The radioactivity on the filters was counted with a LKB gamma counter.

2. CCK Receptor Binding (Brain)

CCK-8 sulphated was radiolabelled and the binding was performed according to the description for the pancreas method with minor modifications.

5 Male Hartley guinea pigs (300-500g) were sacrificed by decapitation and the cortex was removed and homogenized in 25 mL ice-cold 0.32 M sucrose. The homogenates were centrifuged at 1000 g for 10 minutes and the resulting supernatant was recentrifuged at 20,000 g for 20 minutes. The P₂ pellet was resuspended in binding assay buffer (20 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulfonic acid (HEPES), 5 mM MgCl₂, 0.25 mg/ml bacitracin, 1 mM ethylene glycol-bis-(β -aminoethylether-N,N'-tetraacetic acid) (EGTA) pH 6.5 at 10 25°C, using a teflon homogenizer (5 strokes at 500 rpm) to give a final concentration of 10 mg original wet weight 11.2 ml buffer. For the binding assay, 50 μ l of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 μ M (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ¹²⁵I-CCK-8 binding) and 50 μ l of 500 pM ¹²⁵I-CCK-8 (i.e. final concentration of 50 pM) were added to 400 μ l of the membrane suspensions in microfuge tubes. All assays were run in duplicate. The reaction mixtures were 15 incubated at 25°C for 2 hours and then the reaction was terminated on Whatman GF/C filters by rapid filtration (Brandell 24 well cell Harvester) with 3 x 5 ml washes of cold 100 mM NaCl. The radioactivity on the filters was then counted with a LKB gamma counter.

5. Gastrin Antagonism

20 Gastrin antagonist activity of compounds of Formula I is determined using the following assay.

A. Gastrin Receptor Binding in Guinea Pig Gastric Glands

25 Preparation of guinea pig gastric mucosal glands

Guinea pig gastric mucosal glands were prepared by the procedure of Chang et al., Science 230, 177-179 (1985) with slight modification. Gastric mucosa from guinea pigs (300-500 g body weight, male Hartley) were isolated by scraping with a glass slide after washing stomachs in ice-cold, aerated buffer consisting of the following: 130 mM NaCl, 12 mM NaHCO₃, 3 mM NaH₂PO₄, 3 mM Na₂HPO₄, 3 mM K₂HPO₄, 2 mM MgSO₄, 1mM 30 CaCl₂, 5 mM glucose and 4 mM L-glutamine, 50 mM HEPES, 0.25 mg/ml bacitracin, 0.10 mg/ml soya bean trypsin inhibitor, 0.1 mg/ml bovine serum albumin, at pH 6.5, and then incubated in a 37°C shaking water bath for 40 minutes in buffer containing 1 mg/ml collagenase and bubbled with 95% O₂ and 5% CO₂. The tissues were passed twice through a 5 ml syringe to liberate the gastric glands, and then filtered through Nitex #202 35 gauge nylon mesh. The filtered glands were centrifuged at 272 g for 5 minutes and washed twice by resuspension in 25 ml buffer and centrifugation.

B. Binding studies

40 The washed guinea pig gastric glands prepared as above were resuspended in 25 ml of standard buffer. For binding studies, to 250 μ l of gastric glands, 30 μ l of buffer (for total binding) or gastrin (3 μ M final concentration, for nonspecific binding) or test compound and 20 μ l of ¹²⁵I-gastrin (NEN, 2200 Ci/mmol, 0.1 nM final concentration) were added. AV assays were run in triplicate. The tubes were aerated with 95% O₂ and 5% CO₂ and capped. The reaction mixtures after incubation at 25°C for 30 minutes in a shaking water bath were rapidly 45 filtered (Brandell 24 well cell harvester) over Whatman and G/F B filters presoaked in assay buffer and immediately washed further with 3 x 4 ml of 100 mM ice cold NaCl. The radioactivity on the filters was measured using a LKB gamma counter.

In Vitro Results

50 Effect of The Compounds of Formula I on ¹²⁵I-CCK-8 receptor binding

The preferred compounds of Formula I are those which produced dose-dependent inhibition of specific ¹²⁵I-CCK-8 binding as defined as the difference between total and non-specific (i.e. in the presence of 1 μ M CCK) 55 binding.

Drug displacement studies were performed with at least 10 concentrations of compounds of formula 1 and the IC₅₀ values were determined by regression analysis. IC₅₀ refers to the concentration of the compound required to inhibit 50% of specific binding of ¹²⁵I-CCK-8.

The data in Table I were obtained for compounds of Formula I.

TABLE I

CCK RECEPTOR BINDING RESULTS
IC₅₀ (μM)

Compound of Ex #	¹²⁵ I-CCK Pancreas	²⁵ I-CCK Brain	²⁵ I-Gastrin Gastric Glands
1	0.011	0.0079	0.0036
2	500	0.00012	N.D.
3	0.258	0.0589	N.D.
4	0.566	0.010	N.D.

(N.D. = No Data)

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

Synthesis of N-{1,3-Dihydro-1-[1H-4-imidazolyl]methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)-urea].

(A) 4-(Chloromethyl)imidazole hydrochloride (1)

To a solution of 20 ml of toluene containing 2 ml of thionyl chloride was added 700 mg of 4-(hydroxymethyl)imidazole hydrochloride. The reaction mixture was heated to the refluxing temperature of the solvent for 3 hours, cooled and concentrated to dryness under reduced pressure. The title compound was obtained as a white solid (790 mg, 99% yield).

(B) 1-(2,4-Dinitrophenyl)-4-(chloromethyl)imidazole (2)

4-(Chloromethyl)imidazole hydrochloride (790 mg) was dissolved in 20 ml of acetonitrile. To this solution was added 713 μL of 2,4-dinitrofluorobenzene and 2.14 g of potassium carbonate. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate) and concentrated. The crude reaction product was purified by flash silica gel chromatography (8:2 ethyl acetate-hexane elution) to give 745 mg of the title compound.

(C) 1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-4-imidazolyl]-methyl-3-[(benzyloxycarbonyl)amino]-5-phenyl-2H-1,4-benzodiazepin-2-one. (3)

1,3-Dihydro-3(R,S)-[(benzyloxycarbonyl)-amino]-5-phenyl-2H-1,4-benzodiazepin-2-one (186 mg) was dissolved in 3 ml of dry N,N-dimethylformamide at 0°C. To this solution was added 21.2 mg of (60%) sodium hydride and the whole was stirred for 1 hour. 1-(2,4-Dinitrophenyl)-4-(chloromethyl)imidazole in 1 ml of dry N,N-dimethylformamide was then added. The reaction was judged to be 50% complete (TLC) after 0.5 hours at 0°C.

An additional 10.6 mg of (60%) sodium hydride was added and stirring was continued for 0.5 hours more. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and 10% citric acid solution. The organic phase was dried (sodium sulfate), and concentrated. The title compound (75 mg) was obtained in pure form after flash silica gel chromatography employing chloroform-methanol (9:1 v/v) followed by preparative thick layer chromatography on 1 mm precoated silica gel plates (ethyl acetate elution).

(D) 1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-4-imidazolyl]methyl-3-amino-5-phenyl-2H-1,4-benzodiazepin-2-one hydrobromide. (4)

1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-4-imidazolyl]methyl-3-[(benzyloxycarbonyl)amino]-5-phenyl-2H-1,4-benzodiazepin-2-one (70 mg) was dissolved in 10 ml of methylene chloride. The resulting solution was cooled to 0°C and saturated with hydrogen bromide gas for 10 minutes. The reaction vessel was sealed and the reaction mixture was allowed to warm to room temperature over 0.5 hours. The vessel was vented and the solvent and excess hydrogen bromide gas were removed under reduced pressure to give 70 mg of the title compound.

(E) N-{1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-4-imidazolyl]methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)urea]. (5)

1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-4-imidazolyl]methyl-3-amino-5-phenyl-2H-1,4-benzodiazepin-2-one hydrobromide (70 mg) was suspended in 3 ml of dry tetrahydrofuran. To this suspension was added in succession 46.8 µL of triethylamine and 15.9 µL of m-tolylisocyanate. The pH of the reaction mixture was maintained at approximately 8. The reaction mixture was protected from moisture and was allowed to stir at room temperature for 0.5 hours. The reaction mixture was filtered and the filtrate was concentrated to 1 ml under reduced pressure. The residual material was chromatographed on three 0.5 mm x 20 cm x 20 cm precoated silica gel plates (ethyl acetate elution). In this way 43 mg (61%) of the title compound was obtained in analytical form.

(F) N-{1,3-Dihydro-1-[1H-4-imidazolyl]methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)urea]. (6)

N-{1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-4-imidazolyl]methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)urea] (40 mg) was combined with 12.0 µL of thiophenol in 2 ml of dry N,N-dimethylformamide at room temperature. The reaction mixture was stirred for 1 hour and concentrated under reduced pressure to give the crude reaction product as a solid. Purification by preparative thick layer chromatography employing two 0.5 mm x 20 cm x 20 cm precoated silica gel plates (chloroform-methanol, 95:5, v/v elution) afforded the title compound analytically pure: m.p. 240°C (d).

HPLC = 97.6% pure at 214 nm; TLC R_f = 0.44 (CHCl₃-CH₃OH, 9:1).

NMR (DMSO-D₆): Consistent with structure assignment and confirms presence of solvent.

FAB MS: 465 (M⁺ + 1).

Analysis for C₂₇H₂₄N₆O₂ • 0.35 CHCl₃ • 0.95 H₂O:

Calculated: C, 62.75; H, 5.06; N, 16.06.

Found: C, 63.15; H, 5.13; N, 15.06.

EXAMPLE 2

Synthesis of N-{1,3-Dihydro-1-[pyrrolidinecarbonyl]methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-(R)-yl}-N'-[(3-methylphenyl)-urea].

1,3-Dihydro-1-(pyrrolidinecarbonyl)methyl-3(R)-[(α-methyl)benzyloxy-carbonyl]-amino-5-phenyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-phenyl-3(R)-[(α-methyl)benzyloxycarbonyl]-amino-2H-1,4-benzodiazepin-2-one (100 mg, 0.25 mmole) in 2 ml of dry N,N-dimethylformamide was stirred magnetically in an ice bath under an inert atmosphere. Cesium carbonate (106 mg, 0.325 mmole) and pyrrolidinylacetamide (78 mg, 0.325 mmole) were added and the reaction mixture was stirred vigorously at 0° C for 1.75 hours. The reaction mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with brine. The crude product

was chromatographed on three, 1 mm X 20 cm X 20 cm precoated silica gel plates (3:2 hexane-ethyl acetate elution) to give 109 mg of the title compound.

1,3-Dihydro-1-(pyrrolidinylcarbonyl)methyl-3(R)-amino-5-phenyl-2H-1,4-benzodiazepin-2-one hydrobromide

1,3-Dihydro-1-(pyrrolidinylcarbonyl)methyl-3(R)-[(α -methyl)benzyloxy-carbonyl]-amino-5-phenyl-2H-1,4-benzodiazepin-2-one (109 mg) was dissolved in 10 ml of dry methylene chloride. The solution was cooled to 0°C and saturated with hydrogen bromide gas. After 30 minutes the solvent and excess hydrogen bromide were removed under reduced pressure to give 147 mg of the title compound as a pale yellow solid.

N-{3-(R)-1,3-Dihydro-1-(pyrrolidinylcarbonyl)methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3(R)-yl}-N'-{[3-(1H-tetrazol-5-yl)phenyl]urea}.

A solution of 51 mg of 3-amino-(1H-tetrazole-5-yl)benzene in 2 ml of tetrahydrofuran was stirred magnetically in an ice bath and treated in sequence with triethylamine (44 μ L) and triphosgene (31 mg) under anhydrous conditions. The pH of the reaction mixture was adjusted to approximately 8 with the incremental addition of triethylamine. After 15 minutes, a solution of methylene chloride (2 ml) containing 140 mg of 1,3-dihydro-1-(pyrrolidinylcarbonyl)methyl-3(R)-amino-5-phenyl-2H-1,4-benzodiazepin-2-one hydrobromide and one equivalent of triethylamine was added and the reaction mixture was stirred at room temperature for 60 minutes more. The reaction mixture was concentrated under reduced pressure, the residue was partitioned between ethyl acetate/water, and then rendered acidic with 1M HCl solution. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried (sodium sulfate), and roto-evaporated. Preparative thick layer chromatography of the crude reaction product precoated silica gel plates (chloroform-methanol-acetic acid, 94:6:0.6, v/v elution) afforded the title compound (45 mg) as a solid after trituration with ether: m.p. >225° C (d).

HPLC = >98% pure at 214 nm; TLC R_f = 0.54 (CHCl_3 - CH_3OH -HOAc 90:10:1, v/v).

NMR(DMSO- D_6): Consistent with structure assignment and confirms presence of solvent.

FAB MS: 550 (M^+ + 1).

Analysis for $\text{C}_{29}\text{H}_{27}\text{N}_9\text{O}_3 \bullet 0.45\text{Et}_2\text{O} \bullet 0.3\text{CHCl}_3$:

Calculated: C, 60.36; H, 5.18; N, 20.37.

Found: C, 60.42; H, 4.89; N, 20.35.

EXAMPLE 3

Synthesis of N-{1,3-Dihydro-1-[1H-2-imidazolyl]-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-{[3-methylphenyl]-urea}.

2-(Chloromethyl)imidazole hydrochloride

To a solution of 30 ml of toluene containing 3 ml of thionyl chloride was added 970 mg of 2-(hydroxymethyl)imidazole hydrochloride. The reaction mixture was heated to the refluxing temperature of the solvent for 3 hours, cooled and concentrated to dryness under reduced pressure. The residue was resuspended in methylene chloride treated with 2 ml of thionyl chloride and refluxed for 1 hour more. Concentration in vacuo afforded the title compound as a white solid (1.2 g).

1(2,4-Dinitrophenyl)-2-(chloromethyl)imidazole

2-(Chloromethyl)imidazole hydrochloride (920 mg) was dissolved in 5 ml of acetonitrile. To this solution was added 830 μ L of 2,4-dinitrofluorobenzene and 2.5 g of potassium carbonate. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate) and concentrated. The crude reaction product was purified by flash silica gel chromatography (1:1 ethyl acetate-hexane elution) to give 710 mg of the title compound as a yellow solid.

1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-2-imidazolyl]-methyl-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one.

1,3-Dihydro-5-phenyl-3(R,S)-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one (200 mg) was dis-

solved in 3 ml of dry N,N-dimethylformamide at 0°C. To this solution was added 21 mg of (60%) sodium hydride and the whole was stirred for 20 minutes.

1-(2,4-Dinitrophenyl)-2-(chloromethyl)imidazole (161 mg) in 1 ml of dry N,N-dimethylformamide was then added. The ice bath was removed and the reaction mixture was stirred for 30 minutes and quenched with 10% citric acid solution. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and brine. The organic phase was dried (sodium sulfate), and concentrated. The title compound (175 mg) was obtained in pure form after silica gel chromatography employing ethyl acetate-hexane (7:4 v/v).

10 1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-2-imidazolyl]-methyl-5-phenyl-3-amino-2H-1,4-benzodiazepin-2-one.

1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-2-imidazolyl]methyl-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one (155 mg) was dissolved in 10 ml of methylene chloride. The resulting solution was cooled to 0° C and saturated with hydrogen bromide gas for 10 minutes. The reaction vessel was sealed and the reaction mixture was allowed to warm to room temperature over 0.5 hours. The vessel was vented and the solvent and excess hydrogen bromide gas were removed under reduced pressure. The residue was partitioned between ethyl acetate and saturated sodium carbonate solution. The organic phase was dried (Na₂SO₄) and concentrated to give the title compound.

20 N-{1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-2-imidazolyl] methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)urea].

1,3-Dihydro-1-[1-(2,4-dinitrophenyl)-2-imidazolyl]methyl-5-phenyl-3-amino-2H-1,4-benzodiazepin-2-one (125 mg) was suspended in 3 ml of dry tetrahydrofuran. To this suspension was added in succession two drops of triethylamine and 32 µL of m-tolylisocyanate. The pH of the reaction mixture was maintained at approximately 8. The reaction mixture was protected from moisture and was allowed to stir at room temperature for 0.5 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The title compound was dried in vacuo and used directly in the next step without purification.

30 N-{1,3-Dihydro-1-[1H-2-imidazolyl]methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)urea].

Crude N-{1,3-dihydro-1-[1-(2,4-dinitrophenyl)-4-imidazolyl]methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)urea] (0.25 mmole) was combined with 51 µL of thiophenol in 2 ml of dry N,N-dimethylformamide at room temperature. The reaction mixture was stirred for 1 hour and concentrated under reduced pressure to give the crude reaction product as a solid. Purification by preparative thick layer chromatography employing four 0.5 mm X 20 cm X 20 cm precoated silica gel plates (chloroform-methanol-concentrated ammonium hydroxide, 90:10:1, v/v elution) afforded 30 mg of the title compound analytically pure: m.p. 160° C (shrinks).

40 HPLC = >95% pure at 214 nm; TLC R_f = 0.37 (CHCl₃-CH₃OH-NH₄OH, 90:10:1).
NMR(DMSO-D₆): Consistent with structure assignment and confirms presence of solvent
FAB MS: 465 (M⁺ + 1).

Analysis for C₂₇H₂₄N₆O₂•0.15 CHCl₃•1.15 H₂O:

Calculated: C, 64.75; H, 4.94; N, 16.81.

45 Found: C, 64.81; H, 5.30; N, 16.70.

EXAMPLE 4

50 Synthesis of N-{1,3-Dihydro-1-[5-(2-methyl-1,3,4-triazolo)-methylene]-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[(3-methylphenyl)urea].

1,3-Dihydro-1-[2-acetamido]-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one.

55 1,3-Dihydro-5-phenyl-3(R,S)-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one (1.5 g, 3.89 mmole) was dissolved in 15 ml of dry N,N-dimethylformamide at 0° C. To this solution was added 1.65 g of cesium carbonate. After 15 minutes, 473 mg (5.06 mmole) of 2-chloroacetamide was added. The reaction mixture was stirred for 50 minutes at 0° C. More cesium carbonate (160 mg) and 2-chloroacetamide (50 mg) were added and stirring was continued at room temperature. The reaction was judged to be 90% complete (TLC)

after 1 hour. An additional amount of cesium carbonate (160 mg) and 2-chloroacetamide (50 mg) were added. After 2 hours the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 10% citric acid solution. The organic phase was washed with brine, dried (sodium sulfate), and concentrated to give 2.8 g of the title compound as an oil which slowly crystallized on standing.

1,3-Dihydro-1-[N-(N,N-dimethylaminoacetimino)-acetamido]-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one.

1,3-Dihydro-1-[2-acetamido]-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one (138 mg) and N,N-dimethylacetamide dimethylacetal (2 ml) were combined and heated at 100° C for three hours. The reaction mixture was cooled and poured into 20 ml of water and extracted with ethyl acetate. The combined organic extracts were dried (sodium sulfate) and concentrated under reduced pressure to give 217 mg of the crude product which was used in the next reaction step without further purification.

1,3-Dihydro-1-[5-(2-methyl-1,3,4-triazolo)methylene]-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one.

1,3-Dihydro-1-[N-(N,N-dimethylaminoacetimino)-acetamido]-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one (217 mg) was dissolved in 5 ml of acetic acid and treated with 27 μ L of 95% hydrazine. The resulting solution was heated at 90°C for 2.5 hours. The reaction mixture was cooled and poured into 50 ml of water. The aqueous solution was extracted with ethyl acetate (2 x 50 ml) and the combined organic extracts were washed with brine, dried (sodium sulfate), and concentrated under reduced pressure. The oily residue was azeotropically dried with toluene and then chromatographed on silica gel (chloroform-methanol elution, 94: v/v) to give 113 mg of the title compound.

1,3-Dihydro-1-[5-(2-methyl-1,3,4-triazolo)methylene]-5-phenyl-3-amino-2H-1,4-benzodiazepin-2-one.

1,3-Dihydro-1-[5-(2-methyl-1,3,4-triazolo)methylene]-5-phenyl-3-[(benzyloxycarbonyl)amino]-2H-1,4-benzodiazepin-2-one (110 mg, 0.229 mmole) was dissolved in 57.3 ml of methanol containing 2.7 ml of 90% formic acid. To this solution was added under nitrogen 60 mg of 10% palladium/carbon catalyst suspended in 5 ml of the above methanol/formic acid solvent mixture. The resulting reaction mixture was stirred vigorously for 60 minutes at 23°C under nitrogen. An additional 60 mg of the catalyst was added and stirring was then continued at 45°C for 30 minutes more. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The residual oil was then azeotropically dried with toluene, dissolved in 20 ml of ethyl acetate and rendered alkaline with 10% sodium carbonate solution. The phases were separated and the organic layer was washed with brine, dried (Na₂SO₄), and concentrated to give 80 mg of the title compound as its free base.

N-{1,3-Dihydro-1-[5-(2-methyl-1,3,4-triazolo)-methylene]-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl}-N'-[3-methylphenyl]urea.

1,3-Dihydro-1-[5-(2-methyl-1,3,4-triazolo)methylene]-5-phenyl-3-amino-2H-1,4-benzodiazepin-2-one (41.5 mg, 0.12 mmole) was dissolved in 2 ml of dry tetrahydrofuran and the solution was cooled to 0°C.

To this solution was added 15.5 μ L of m-tolylisocyanate. After 10 minutes at 0°C, TLC analysis indicated that the starting materials had been consumed. The reaction mixture was concentrated to 1 ml under reduced pressure and the residual material was chromatographed on three 0.5mm X 20cm X 20 cm precoated silica gel plates (chloroform-methanol elution, 9:1 v/v). In this way 13 mg of the title compound was obtained in analytically pure form: m.p. 172°C(d).

TLC R_f = 0.17 (CHCl₃-CH₃OH, 9:1).

NMR(DMSO-D₆): Consistent with structure assignment and confirms presence of solvent.

FAB MS: 480 (M⁺ + 1).

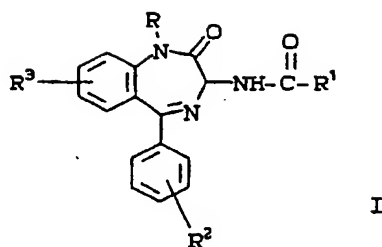
Analysis for C₂₇H₂₅N₇O₂•0.30 CHCl₃•0.85 CH₃OH:

Calculated: C, 62.31; H, 5.33; N, 18.07.

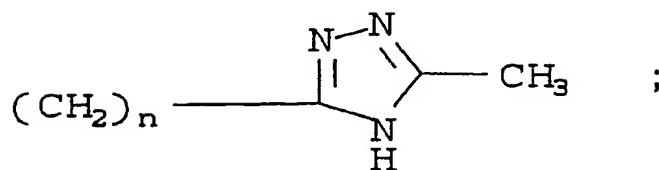
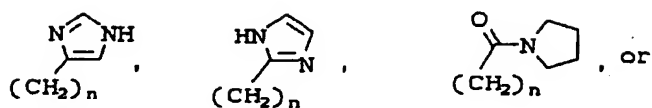
Found: C, 62.62; H, 4.97; N, 17.70.

Claims

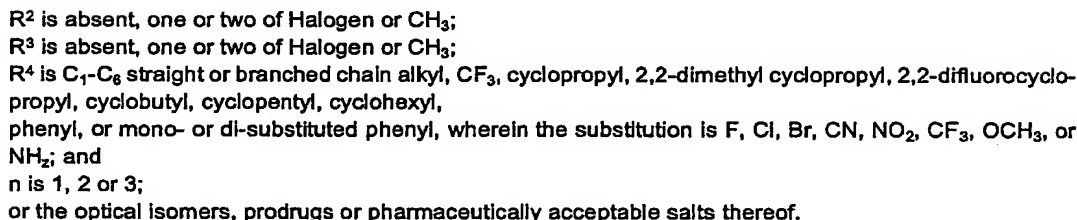
1. A compound of Formula I:



wherein:
R is



R¹ is



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6. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for treating panic disorders in a mammal.
- 5 7. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for treating gastrointestinal diseases in a mammal.
8. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for treating central nervous system disorders in a mammal.
- 10 9. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for treating oncologic disorders in a mammal.
10. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for preventing or treating the withdrawal response produced by chronic treatment or abuse of drugs or alcohol in a mammal.
- 15 11. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for inducing miosis following intraocular examinations or surgery in a mammal.
12. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for inducing analgesia in a mammal.
- 20 13. The use of a compound of claim 1 or claim 2 for the manufacture of a medicament for preventing or treating neurodegenerative disorders in a mammal.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 3192

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,X	EP-A-0 284 256 (MERCK & CO. INC.) * the whole application, particularly examples 236 and 284 *	1-13	C07D243/24 C07D403/06 C07D401/12 C07D403/12 C07D401/14 C07D403/14 A61K31/55
D,X	JOURNAL OF MEDICINAL CHEMISTRY vol. 32, no. 1, January 1989, WASHINGTON US pages 13 - 16; M.G. BOCK ET AL.: 'Benzodiazepine gastrin and Brain Cholecystokinin Receptor Ligands: L-365,260' * the whole article, particularly page 15, table I, compound 8 *	1-13	
P,X	WO-A-9 201 683 (FUJISAWA PHARMACEUTICAL CO., LTD.) * the whole application, particularly example 7(10) *	1-13	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C07D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 08 JULY 1992	Examiner ALLARD M.S.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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